objected-to phrase, and particularly the phrase "distal to the lymphatic system" are clear and definite. However, in order to advance the prosecution of the case, Applicants have cancelled Claim 1. The new and amended claims do not include the objected-to phrase. Therefore, Applicants submit that the rejection under § 112, second paragraph, is now moot.

Discussion Of Rejection Under 35 U.S.C. § 102

The Office Action rejected Claims 1, 4, 7-10, 14, 39, 43-52, 55-59, and 61-70 under 35 U.S.C. § 102(b) as being anticipated by Martins et al. ("Martins") (U.S. Patent No. 4,455,142). To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986).

As discussed above, Claim 1 has been cancelled without prejudice to future prosecution, and new independent Claims 72, 79, 82, 83, and 87 have been added. Respectfully, Applicants assert that Martins fails to teach each and every element of new Claims 72, 79, 82, 83, and 87, and the claims depending therefrom.

Martins Is Not A Proper Reference Under 35 U.S.C. § 102

Applicants maintain that Martins is inappropriate as a § 102 or a § 103 reference because it completely fails to teach or even suggest cytotoxic T lymphocytes (CTL). Inducing and sustaining a CTL response is a feature of all of the newly pending claims, and Martins provides no teaching or suggestion of CTL. Martins discloses a method consisting of administering antigen with immunopotentiator. *See* Martins at the Abstract and at column 3, lines 26-29, for example. The Martins discussion of provoking an immune response specifies that the provoked immune response can consist of "either the elaboration of antibody or the development of cell-mediated immunity" (emphasis added). *See* Martins at column 3, at lines 54-57. Three of Martins' four examples only demonstrate the elaboration of antibody. *See* Examples 1-3. Example 4 also is primarily concerned with the elaboration of antibody. *See* Example 4. Example 4 also tests for delayed type hypersensitivity (DTH) and fails to find it. *See id.* DTH involves cell-mediated immunity and T cells. However, DTH is primarily a helper T cell phenomenon. Helper T cells are not the same as CTL, and their abilities to respond to any

particular antigen will differ. *See Fundamental Immunology* 4th Ed. by Paul, published by Lippincott-Raven 1999, p1360, col. 2, 2nd full paragraph, 2nd sentence; or more extensively *Immunobiology* 2nd Ed. by Janeway and Travers, Published by Current biology/Garland Publishing 1996, pp.4:2-4:3 and *Immunology* 3rd Ed. by Kuby, published by W.H. Freeman and Co. 1997, pp.253-260.

"Cell-mediated immunity" and "T cell" are broader terms than "CTL." Reference to cell-mediated immunity or to T cell does not necessarily equal a reference to CTL. The distinctions among the various types of cell-mediated immunity and the various T cells cannot be overstated. Each type of cell-mediated immunity and T cell is unique, with different challenges and characteristics. Each is the subject of separate in-depth scientific study with separate bodies of literature. A method for obtaining one does not necessarily result in obtaining another. If Martins does teach or suggest, and enable any specific type of cell-mediated immunity at all, it does not teach or suggest or enable CTL. The only example of cell-mediated immunity in Martins, found in Example 4, is delayed type hypersensitivity, which is classically a helper T cell response. *See* column 4, lines 57-58 and Example 4. As discussed above, CTL are not equivalent to the helper T cells suggested by DTH reactions. Moreover, Martins failed to detect a cell-mediated response. *See* Martins at column 13, lines 64-65.

In addition to helper T cells implied by a DTH reaction, Martins also makes multiple references to specific types of immunities and immune cell types. *See for example,* column 2, lines 22-25; column 3, lines 54-57; column 4, line 47; column 4, lines 58-60; column 8, line 7; column 9, line 11; and column 9, lines 56-63. However, despite specific mention of these other immunities and immune cells, a discussion of CTL is conspicuously absent from Martins.

Applicants have taught that induction of CTL and sustaining CTL effectively is a challenging task, particularly for anti-tumor and antimicrobial applications. *See* specification at page 1-5. Applicants have provided great detail regarding the requirements for obtaining a sustained CTL response. *See* specification generally. Respectfully, it is difficult to imagine that Martins, without even specifically mentioning CTL, can be considered as a reference that teaches or suggests and enables inducing a CTL response or sustaining a CTL response. Martins is not an appropriate reference for anticipating any of the claims and as such no *prima facie* anticipation exists. However, regardless of whether the Examiner properly appreciates the

disclosure of Martins with regard to its lack of teaching regarding CTL, the new Claims also include additional limitations not taught by Martins, as set forth below.

The New Claims Include Features Not Disclosed In Either Martins Or Kündig

New Claim 72 relates to a method of obtaining a sustained CTL response in a mammal. The method includes delivering an antigen directly to a lymph node or lymph vessel of the mammal at a level sufficient to induce a CTL response in the mammal, and maintaining the antigen in the mammal's lymphatic system over time sufficient to sustain the CTL response. As one example, Martins does not disclose direct delivery of antigen to a lymph node or lymph vessel of the mammal. Martins only discloses intramuscular, subcutaneous, intraperitoneal, nasal, ocular, vaginal, and alimentary tract delivery. *See* Martins at column 6, lines 21-25.

New Claim 79 relates to a method of obtaining a sustained CTL response in a mammal. The method includes selecting an antigen suitable for a CTL response in the mammal, delivering the antigen to a lymphatic system of the mammal at a level sufficient to induce a CTL response in the mammal, causing sustained exposure of the antigen to the mammal's lymphatic system, obtaining a sustained CTL response in the mammal, and detecting the sustained CTL response in the mammal. Martins does not teach, for example, selecting an antigen suitable for sustaining a CTL response in the mammal. *See* Martins at column 3, line 49 bridging column 4, line 40. In contrast the instant specification discloses numerous teachings regarding selection of antigen that is suitable for sustaining a CTL response. *See* specification at page 8, first full paragraph and pages 14-55 ("A key aspect of this invention is the delivery of an appropriate antigen to the lymphatic system"). Not every antigen is capable of inducing a CTL response. Many factors can influence whether a CTL response can be sustained by an antigen. Martins also does not teach obtaining a sustained CTL response or detecting a sustained CTL response in the mammal. This is not surprising because Martins does not even mention CTL, much less obtain or detect any sort of CTL response.

New Claim 82 relates to a method of obtaining a sustained CTL response in a mammal. The method includes selecting an antigen that is capable of inducing CTL in a mammal, delivering the antigen to the mammal at a level sufficient to induce a CTL response in the mammal, wherein the antigen is delivered to an area of high lymphatic drainage in the mammal,

and maintaining the antigen in the mammal's lymphatic system sufficient to sustain the CTL response for a period of time that is substantially co-extensive with the desired duration of the CTL response. Martins does not teach, for example, delivering antigen to an area of high lymphatic drainage. *See* Martins at column 6, lines 21-25 (other routes of administration disclosed, but administration to an area of high lymphatic drainage is absent).

New Claim 83 relates to a method of obtaining a sustained CTL response in a mammal. The method includes delivering an antigen to a lymphatic system of the mammal at a level sufficient to induce a CTL response in the mammal, causing sustained exposure of the antigen to the mammal's lymphatic system, obtaining a sustained CTL response in the mammal, and detecting the sustained CTL response in the mammal. Again, as already discussed above, for example, Martins does not teach obtaining a sustained CTL response, or detecting a sustained CTL response in the mammal.

New Claim 87 relates to a method of obtaining a sustained CTL response in a mammal. The method includes delivering an antigen in an acellular composition directly to an area of high lymphatic drainage in the mammal at a level sufficient to induce a CTL response in the mammal, and maintaining the antigen in the mammal's lymphatic system over time sufficient to sustain the CTL response. Martins does not teach, for example, delivering antigen in an acellular composition directly to an area of high lymphatic drainage. As mentioned above, Martins at column 6, lines 21-25 provides a discussion regarding routes of administration, and these teachings do not include or suggest delivering antigen to an area of high lymphatic drainage.

For all of the above reasons, Applicants respectfully submit that Martins does not anticipate any of the pending claims. Accordingly, Applicants request allowance of all pending claims.

Discussion Of Rejection Under 35 U.S.C. § 103

The Office Action rejected Claims 2, 3, 5-6, 11-13, 15-16, and 20-21 under 35 U.S.C. § 103(a) as being unpatentable over Martins as applied to Claims 1 and 4 under § 102(b) above in view of Kündig (*Science*, 268:1343-1347). Claims 17-19, 41-42, and 53-54 were rejected under § 103(a) as being unpatentable over Martins, as applied above to Claims 4, 39 and 48 under § 102(b), and further in view of Falo, Jr., et al. ("Falo Jr.") (U.S. Patent No. 5,951,975).

Further, the Office Action rejected Claims 40 and 60 under § 103(a) as being unpatentable over Martins as applied to Claims 39 and 59 above under § 102(b), and further in view of Eberlein et al. ("Eberlein") (U.S. Patent No. 5,550,214).

There Is No Proper *Prima Facie* Case Of Obviousness Under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the primary reference. Second, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Third, the prior art reference must teach or suggest all the claim limitations. *See* M.P.E.P. §2143; *In re Royka*, 490 F.2d 981 (CCPA 1974).

"Obviousness can not be established by hindsight combination to produce the claimed invention.. . . [I]t is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination." *In re Dance*, 160 F.3d 1339 (Fed. Cir. 1998). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999); *see also Epochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000).

The combination of Martins and Kündig is nonobvious. An effort to construct a *prima facie* case of obviousness would require the impermissible benefit of hindsight. Several inadequacies of Martins as a primary reference have been discussed above. Kündig demonstrated that fibroblasts can act as antigen presenting cells and induce CTL in the spleen. *See* Kündig at page 1344-45. Kündig's experiments were designed to show that cells other than antigen presenting cells can induce CTL. "We now show that transfected fibroblasts lacking costimulatory function but expressing a class I-associated virus peptide could directly and efficiently induce CTL responses" (emphasis added). Kündig at 1345. Kündig did not teach or suggest maintaining antigen to sustain a CTL response.

Applicants maintain this argument in connection with the prior rejections under § 103, although those rejections are moot in light of the new claims. The following arguments are in support of the new claims.

Martins And Kündig Do Not Teach Or Suggest All Of The Claim Limitations

Martins and Kündig alone or combined do not disclose or suggest the combination of limitations in the claims. As discussed above, Martins fails to teach or even suggest each and every element of the independent claims. Martins, even if combined with Kündig or any of the other cited references, fails to teach or suggest all of the features of the claims. Kündig does not provide the missing features for any of the claims.

New Claim 72 is not obvious over Martins when combined with Kündig because the references, alone or in combination, do not teach or suggest direct delivery to a lymph node or a lymph vessel. Kündig, like Martins, fails to teach or suggest maintaining antigen in the mammal's lymphatic system over time sufficient to sustain the CTL response. Therefore, Claim 72 and its dependent claims are not obvious over Martins in view of Kündig.

New Claim 79 is also not obvious over Martins when combined with Kündig. Martins, even combined with Kündig fails, for example, to teach or suggest selecting an antigen suitable for sustaining a CTL response in the mammal. Also, as another example, the references fail to disclose obtaining a sustained CTL response in the mammal, and also detecting the sustained CTL response in the mammal. Thus, Claim 79 and its dependent claims are not obvious over Martins in view of Kündig.

Further, Martins combined with Kündig fails to teach or suggest all of the limitation of new Claim 82. For example, neither reference discloses or recognizes the advantage of delivery to an area of high lymphatic drainage and neither teaches the maintaining step to sustain the CTL response. In contrast, the instant application at pages 60-61 explains that a patient's lymphatic flow can be assessed to determine where relatively high lymphatic drainage occurs for optimum antigen delivery. Thus, Claim 82 and its dependent claim are not obvious over Martins in view of Kündig.

Also, Martins and Kündig combined fail to teach or suggest all of the limitations of Claim 83. For example, without limitation, as discussed above, the references do not teach or suggest obtaining a sustained CTL response. They also do not disclose detecting a sustained CTL response. Therefore, Claim 83 and its dependent claims are not obvious over Martins in view of Kündig.

Finally, the combination of references does not teach or suggest all of the limitations of Claim 87. As one example, neither Martins nor Kündig discloses delivering antigen in an acellular composition directly to an area of high lymphatic drainage. Further, the maintaining step is also lacking as discussed above. As a result, Claim 87 and its dependent claims are not obvious over Martins in view of Kündig.

There Is No Motivation To Combine Martins And Kündig

Furthermore, there is no suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the primary reference. Respectfully, it appears that the Examiner has used impermissible hindsight to attempt to reconstruct the previously claimed subject matter.

First, the instant art is very specialized and detailed. The skilled artisan would not find motivation or suggestion to modify a non-CTL reference, Martins, with a reference interested in the specifics of CTL induction, Kündig. Kündig is not relevant to any of the specifically illustrated or mentioned immune responses of Martins, namely, NK cells, complement, B cells, and T cells, such as helper cells. There is no suggestion or motivation in the art to combine the references.

One principle of operation of Martins is that by administering small doses of antigen plus immunopotentiator, one can produce an immune response without provoking the inflammation associated with the normal use of immunopotentiators. *See* Martins at column 2, lines 53-57. With Kündig, such immunopotentiators are not even needed because of delivery to the cytokine-rich spleen. *See* Kündig at page 1345. Modifying Martins with Kündig would change the principle of operation of Martins by making the immunopotentiator a non-requirement to produce an immune response, and perhaps even result in unwanted inflammation due to the presence of immunopotentiator, such as lipopolysacharide, in the lymphoid spleen. This change in operation demonstrates that the combination of Martins with Kündig is not *prima facie* obvious. *See* M.P.E.P. § 2143.01, last paragraph.

Martins was not successful at inducing and sustaining CTL or at teaching the public how to do so, as is evidenced by the continued need for effective CTL induction and sustenance against tumors and infectious disease. More than 20 years have passed since Martins was filed,

and the need for effective CTL induction and sustenance continues to exist. The instant application has been assigned to CTL ImmunoTherapies Corp., a corporation with close to 100 employees. CTL ImmunoTherapies Corp. was founded, attracted investment, and initiated clinical trials based in part upon the technology of the instant application. Such considerations provide persuasive support for the lack of success of Martins at inducing and/or sustaining CTL, and the nonobviousness of the combination of Martins and Kündig, because if Martins had been successful at solving the problems that CTL ImmunoTherapies Corp. exists to solve, CTL ImmunoTherapies Corp. would have had much greater difficulty in receiving funding, and supporting important clinical trials based upon the instant technology. The present state of immunology technology and the great interest in successfully inducing sustained CTL responses stand as persuasive evidence that Martins and Kündig, alone or in combination, failed to disclose or suggest an adequate approach to obtaining a sustained CTL response.

For the reasons set forth above, Claims 72-91 are not obvious over Martins in view of Kündig. Falo Jr. and Eberlein do not disclose the features of the claims lacked by Martins and/or Kündig. Therefore, Applicants respectfully request prompt allowance of all pending claims.

Summary

Applicants have argued and presented facts in support of the following points:

(1) Martins provides no teaching or suggestion of CTL.

(2) There is no suggestion or motivation to combine Martins and Kündig.

(3) Even more important, regardless of whether the Examiner agrees with Applicants' arguments regarding the lack of CTL teaching or the lack of suggestion/motivation to combine, Applicants have also presented claims that are fully patentable . Each independent claim recites at least one feature that is not present in Martins and Kundig individually or combined. Those features include:

- delivering antigen directly to a lymph node or lymph vessel of a mammal at a level sufficient to induce a CTL response in the mammal.
- detecting a sustained CTL response in the mammal.

- delivering the antigen to the mammal at a level sufficient to induce a CTL response in the mammal, wherein the antigen is delivered to an area of high lymphatic drainage in the mammal.
- delivering an antigen in an acellular composition directly to an area of high lymphatic drainage in the mammal at a level sufficient to induce a CTL response in the mammal.

Because all of the foregoing claim features are absent from Martins and Kündig, and because the all of pending Claims 72-91 include at least one of these features, pending Claims 72-91 are immediately allowable.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Final Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 12/18/02

By: Marc T. Morley

Marc T. Morley
Registration No. 52,051
Attorney of Record
Customer No. 20,995
(619) 235-8550

S:\DOCS\MTM\MTM-3682.DOC
121802